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# CLINICAL RESEARCH STUDIES

**From the American Venous Forum**

# Myths, mystique, and misconceptions of venous disease

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Serving as President of the American Venous Forum has been a privilege and a great honor. All who have been and will be elected president deliberate long and hard about the address they will give, hoping to find inspiration, with the desire that the observations, insight, and information presented will last beyond the time allotted in the program. I hope that the title of this address and the issues discussed will stimulate some and challenge others to extend their efforts to learn, educate, and investigate venous disease.

Defining the terms we use in daily communication is important for clarity of expression and understanding. Misunderstanding frequently occurs when a word used is defined differently by the persons involved. According to *Merriam-Webster's Collegiate Dictionary* (10th edition), a myth is "… a person or thing having only an imaginary existence." Mystique is "… an air or attitude of mystery and reverence developing around something or someone." And misconception is "… bad or wrong, opposite or lack of … (concept)."

For many years venous disease has been relegated as the "stepchild" of vascular surgery. Patients with chronic venous insufficiency were referred to the "clinic" to be cared for by medical students and residents who were often overseen by an uninterested attending staff.

Fortunately, perception and attitudes are changing. The American Venous Forum has stimulated and rewarded intellectual contributions, at both the clinical and basic science level, thereby advancing the field. However, organizations with a special interest in venous disease represent a preciously small percentage of clinical practitioners. Observing current practice, even at major medical centers, it is evident that nearly all facets of venous disease are misunderstood by many, and most persons do not have a grasp of venous disease in its entirety, as it relates to both acute and chronic problems.

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## VENOUS DISEASE IS INCREDIBLY DIFFICULT AND COMPLEX

The first misconception is that "venous disease is incredibly difficult and complex." This quote was recently articulated at a national meeting by a recognized authority in vascular disease and an expert in venous disease. Such statements made by recognized experts disenfranchise the less well informed and erase enthusiasm for pursuing an understanding of venous disorders. I believe that reference was being made to patients with chronic venous insufficiency, although many physicians believe that acute venous thrombotic disorders are also complex. It is my opinion that venous disease is simple, in both the acute and chronic forms. For acute venous thrombosis, we need to understand the etiology of deep venous thrombosis (DVT) to offer effective prophylaxis and understand the natural history to integrate current treatment options to reduce post-thrombotic consequences. In patients with chronic venous insufficiency, we need to merely understand the underlying pathophysiology so that appropriate management can be offered.

I will begin with a quick look at chronic venous insufficiency and the post-thrombotic syndrome. The pathophysiology has been elucidated by previous investigators, and exercise-induced venous hypertension appears to be the common denominator in the majority of patients.[1,2] Only two problems occur in the venous system that contribute to exercise-induced or ambulatory venous hypertension, and they are valvular incompetence and venous obstruction. Once the underlying pathophysiologic parameters are identified, we can either begin a therapeutic strategy to correct the abnormal physiology or accept it and manage the symptomatic outcome, ie, the chronic venous insufficiency syndrome. Technology offers us the

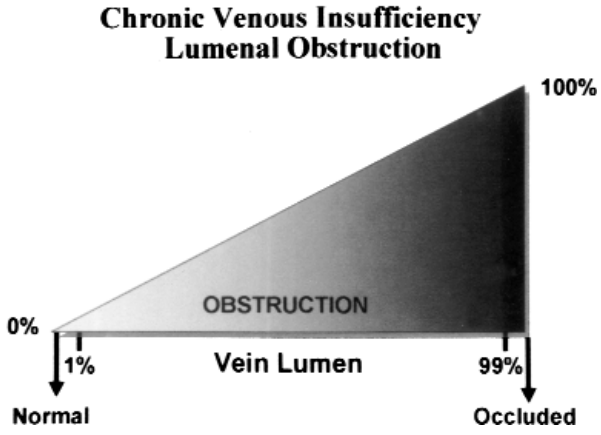


**Fig 1.** Obstruction of the vein lumen, which contributes to chronic venous insufficiency, should be viewed conceptually as any compromise of the vein lumen between 1% and 99%. Complete obliteration of the vein lumen is occlusion.

opportunity to clearly evaluate venous valve function, in both the superficial and deep veins, from the inguinal ligament to the ankle. Unfortunately, our ability to diagnose and quantify obstruction is severely limited.

## VENOUS OBSTRUCTION CAN BE DIAGNOSED AND QUANTIFIED

Another myth of venous disease is that deep venous obstruction can be adequately diagnosed or quantified. As I reflect upon discussions and deliberations with colleagues, it is apparent that venous "obstruction" as a concept is part of the mystique and misconception of chronic venous disease. Obstruction is often conceptually defined as occlusion! In reality, obstruction should be viewed in a linear sense (as a spectrum) rather than "all or none" (Fig 1). If the vein lumen is not compromised, it is normal, whereas obliteration of the lumen is occlusion. Everything between 1% and 99% luminal compromise is "obstruction." Important questions that are not yet answered include the following:

1. At which point does obstruction impact venous return?
2. At which point can obstruction be detected?
3. What method/technique will be accepted as definitive?

An example of the misconception of obstruction is illustrated by the patient with the post-thrombotic syndrome who underwent an ascending phlebogram which was read as: "… the classic tree-barking appearance of chronic venous disease, but there is no evidence of obstruction" (Fig 2). A standard 3-second maximal venous outflow test with an impedance plethysmograph was obtained, and the value fell within the normal range; therefore, all involved in the care of this patient agreed that "obstruction" was not part of his problem.

A classic Linton procedure was performed, and the femoral vein in the thigh was ligated and divided just below the profunda. After examining the cross-sectional image, it was apparent that although recanalization had occurred, considerable luminal obstruction existed, which did not become physiologically important until the patient exercised.

The fundamental misconception is that obstruction must be anatomically obvious and luminal obliteration complete. Although venous obstruction is often anatomically apparent, it should be defined physiologically. Standard maximal venous outflow studies are poor indicators of obstruction, especially for chronic disease. The underlying pathophysiology in these patients occurs when they are upright and exercising. However, we measure maximal venous outflow in the resting patient in the supine and leg-elevated position. This is fundamentally inconsistent. It appears that we are promoting this misconception by accepting phlebogram interpretations of scarred and recanalized veins as showing no obstruction and by accepting maximal venous outflow results as definitive.

Raju and Fredericks[5] have thoughtfully sought to evaluate venous obstruction in the lower extremity on a physiologic basis by using the arm-foot venous pressure differential at rest and after postocclusive reactive hyperemia. This is an important contribution in the evaluation of the role of venous obstruction in our patients. Unfortunately, most of us do not incorporate these measurements in our practice because they are cumbersome and time-consuming, require physicians to perform the procedures, and, of course, are uncomfortable for the patient. The challenge is to develop a physiologic method to evaluate obstruction that is noninvasive and patient friendly and can be performed by vascular laboratory personnel. There is little doubt that thoughtful members of this society or others in our profession can successfully accomplish this goal, or at least make major strides in this direction.

The myths and misconceptions of acute venous disease are perhaps more subtle, but prevalent nonetheless. Our ability to diagnose venous thromboembolic disease has never been better, yet the choice and method of treatment, duration of treatment, and even whether some patients should be treated at all are continually argued by physicians. The etiology of acute DVT is mystique for some, whereas others have a poor or nonexistent understanding of the genesis of venous thrombosis.

## VALVE CUSP HYPOXEMIA LEADS TO ENDOTHELIAL DAMAGE AND DVT

It has been well established that the majority of "spontaneous" venous thrombi begin within the valve cusp.[6] Localized hypoxemia of venous endothelium within the valve cusp has been proposed and accepted by some researchers as an important etiologic factor. Hamer et al[7] reported their findings after measuring $pO_2$ endoluminally and in the valve pockets of veins in two patients and eight dogs. Under conditions of constant flow, the blood within the valve pockets rapidly became hypoxic, whereas the $pO_2$

within the valve cusp in veins with pulsatile flow was similar to that of luminal blood. The two patients studied in this experiment were undergoing excision of varicose saphenous veins, and the valve cusp studied was within 5 to 10 cm of the saphenofemoral junction. In several animal specimens, endothelial injury and valve cusp thrombus were observed. Although the microelectrodes probed the valve cusp to become properly positioned, thereby potentially causing direct endothelial injury, the authors suggested that the endothelium covering the valve cusps is dependent on luminal blood flow for its oxygen supply, and when they become hypoxic, endothelial damage occurs, setting the stage for thrombosis. Hamer and colleagues did not address the obvious clinical question, why isn't DVT associated with clinical conditions of profound hypoxemia? Professor Hamer was a visiting professor in the Thrombosis Research Center at Temple University in the mid 1980s, during which time similar experiments were performed. Unfortunately, the results could not be duplicated.

There is an alternative theory explaining why venous thrombosis originates in the valve cusp, which has basic experimental validation and direct human clinical correlation. The theory is that venous endothelial damage occurs as a result of venodilatation. The experiments performed to test this theory involved animals and patients undergoing surgical procedures. The endothelial damage occurs in valve cusps, which are usually in an area of the vein wall that is attenuated and thus susceptible to damage. Anatomic studies have demonstrated marked thinning of the vein wall in the area of side branches, which are adjacent to valve cusps.[8]

Dr Gwendolyn Stewart, with whom I had the privilege of collaborating early in my career, developed the hypothesis that venous endothelial damage occurred in veins distant from the site of operation, and that this damage was related to operative venodilation resulting from the trauma of the procedure.[9,10] This work originally investigated the canine model of total hip replacement and major abdominal operations. Animals undergoing operation and nonoperative controls were perfusion-fixed with formaldehyde, and their jugular veins and femoral veins were harvested (Figs 3 and 4). Animals on which surgery was performed had substantially greater endothelial damage compared with the controls, and this damage uniformly occurred within the valve cusp.

A specially designed ultrasound probe was constructed to continuously monitor venous diameter during the operative procedure. Animals that had significant venodilation during the operation had significantly greater endothelial damage than those that had minimal or no operative venodilation.[11]

We extended this experiment to human patients undergoing total hip reconstruction,[12] and subsequently total knee reconstruction,[13] using postoperative phlebograms (DVT) as the endpoint. The cephalic vein opposite the hip on which surgery was performed was continuously monitored, and venous diameter was recorded during the operation. Patients were randomized to receive the venotonic agent dihydroergotamine heparin or placebo preoperatively and postoperatively. All patients had postoperative ascending phlebography. The results showed significant correlation of operative venodilatation with postoperative DVT. Patients who developed DVT had a mean operative venodilatation of 29% compared with only 11% for patients who did not develop postoperative DVT ($P = .0012$).[12] Interestingly, there appeared to be two groups of patients, those who had pronounced operative venodilation and those who had minimal venodilatation. In the group dilating less than 20% of their baseline diameter, postoperative DVT developed in only 17% of patients. In patients who dilated more than 20% of their baseline diameter, phlebographically proven DVT developed in 100%. Interestingly, older patients had greater operative venodilation and a higher incidence of postoperative DVT.

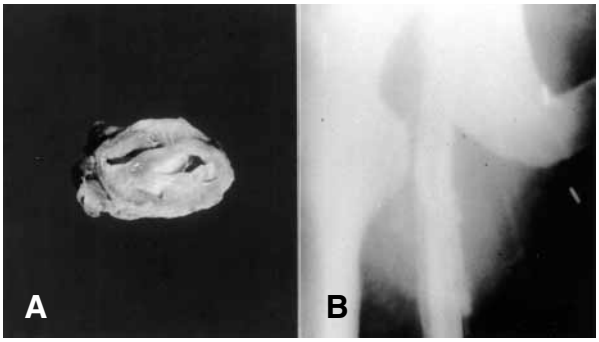


**Fig 2. A,** Cross-section photograph of the proximal femoral vein of a post-thrombotic man with venous ulceration who had a classic Linton procedure performed. The femoral vein below the profunda femoris vein was ligated and divided. Note multiple-channel recanalization of vein lumen; however, a large percentage of the vein lumen is "obstructed." **B,** An ascending phlebogram of the patient's leg preoperatively shows the recanalized femoral vein; however, the official interpretation indicated that there was "chronic disease but no evidence of obstruction."

Patients who underwent total knee replacement had minimal operative venodilatation (with the exception of one outlier), yet had a very high incidence of postoperative DVT (82%). At first glance this might seem to contradict the theory of humorally mediated venodilatation resulting in venous endothelial damage. However, understanding that a thigh tourniquet is applied to the affected leg before skin incision and released after the operation is complete, one realizes that there is no direct circulating correction of the wound with the patient's body. Therefore, if venodilatation is humorally mediated, patients undergoing total knee reconstruction should not have operative venodilatation in distant veins because the products of tissue injury do not escape the leg during the procedure. This was the experimental observation. The expected clinical correlation followed, that ipsilateral DVT after total knee replacement is common but contralateral DVT is unusual.

The hypothesis is that vasoactive mediators, which are products of tissue injury, are produced at the wound, enter

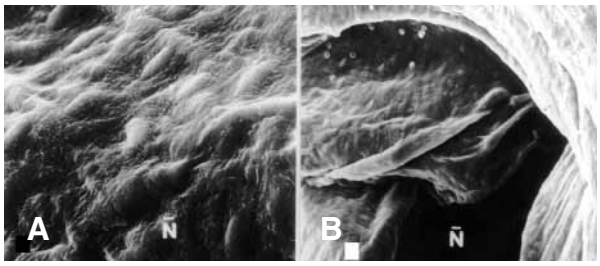


**Fig 3.** Scanning electron micrograph of the jugular vein of a dog that had 6 hours of general anesthesia but no operation. Jugular vein dilated minimally (<10% of baseline diameter) during the experiment. **A,** High-power magnification showing a smooth, intact endothelial monolayer. **B,** Lower-power magnification showing normal endothelium and a normal valve cusp (N).

the blood stream, and survive long enough to have an effect on venous smooth muscle in veins distant from the site of the operation. This vasodilatory response results in endothelial damage, most frequently in the area of the valve cusp, because of attenuation of the wall in this area. This fits with the observations of Sevitt and Gallagher,[6] that thrombus originates within the valve cusp. I believe that this theory also explains the results of the radioactive fibrinogen uptake tests (RFUTs) that had been used to evaluate DVT in postoperative patients. The RFUT has been associated with a large number of false positives when compared with postoperative phlebography, especially in calf veins. It is likely that the radioactive fibrinogen is bound to the areas of endothelial injury in the valve cusp; however, many of the injured sites did not result in phlebographically visible thrombosis, explaining the discrepancy between these studies. Because valves are more prevalent in the calf veins than in the proximal veins, the chance of this observation occurring in calf veins is increased.

## THE SUPERFICIAL FEMORAL VEIN IS SUPERFICIAL

When venous thrombosis is located in the lower extremity between the popliteal and common femoral veins, we say that the "superficial femoral vein" is involved. Although those of us in the vascular specialties recognize that the superficial femoral vein is the major deep vein in the thigh, we are promoting the misconception that the patient has "superficial venous thrombosis" by using this term. This misconception is dangerous because of the potential ramifications of nontreatment of proximal DVT.

Our former president, Dr John Bergan, spearheaded an important study that culminated in the paper "The superficial femoral vein: A potentially lethal misnomer".[14] He and his associates surveyed family physicians and internists, chairpersons of the departments of anatomy, and directors of noninvasive vascular laboratories. They found that only 24% of clinicians would treat patients for DVT if they knew their patient had blood clots in the superficial femoral vein. Only 3% of the anatomists thought the term "superficial femoral vein" was correct, although 22% thought it was acceptable. Only 9% taught this term to medical students. Therefore, although 91% of anatomy courses teach otherwise, 93% of the vascular laboratories use the term "superficial femoral vein" when reporting results of lower-limb venous duplex examinations.

It appears that it was not until 1941 that the term "superficial femoral vein" referred to the vein corresponding to the superficial femoral artery in the thigh. Homans[15] described ligation and division of deep veins to prevent pulmonary emboli in patients with DVT. Since then, these terms have become accepted and used with increasing frequency by vascular surgeons, vascular interventionalists, and vascular laboratories.

Referring to the standard textbook, *Gray's Anatomy*,[16] one cannot find the term *superficial femoral vein*. The book states, "The femoral vein is that which accompanies the femoral artery through the proximal ⅔ of the thigh. It receives numerous muscular tributaries and about 4 cm below the inguinal ligament is joined by the V. profunda femoris; near its termination it is joined by the great saphenous vein."[16]

A frequently read and studied anatomy text is *Clinical Anatomy* by Ellis.[17] It refers to the veins of the lower extremity as "…deep and superficial groups according to their relationship to the investing deep fascia of the leg. The deep veins accompany the corresponding major arteries. The superficial veins are the long and short saphenous veins and their tributaries." [17]

Therefore, it appears that we have no one to blame but ourselves for propagating the misconception that what we refer to as the "superficial femoral vein" is truly superficial. I propose that we abandon this term, and for those of us who are involved with vascular laboratories, that we remove it from our reporting nomenclature. I am certain that this will improve patient care by transmitting accurate information to the referring physician, and patients with DVT extending into the thigh will be appropriately managed.

## CALF-VEIN THROMBOSIS IS CLINICALLY UNIMPORTANT

A common misconception is that isolated calf-vein thrombosis is inconsequential. Natural history studies have demonstrated that patients with isolated calf-vein thrombosis have a higher frequency of post-thrombotic symptoms.[18] Many of us are aware of the occasional high-profile patient who has isolated calf-vein thrombosis and receives instruction to return in 3 to 4 days for a repeat venous duplex evaluation. Before returning, the patient collapses as a result of a massive or, occasionally, fatal, pulmonary embolism. While none of us would presume that the calf clot was responsible for the pulmonary embolism and certainly not for a fatal pulmonary embolism, calf DVT was unquestionably a marker for more extensive thrombosis elsewhere, most likely in the proximal nonaxial veins. Some of the issues contributing to the miscon-

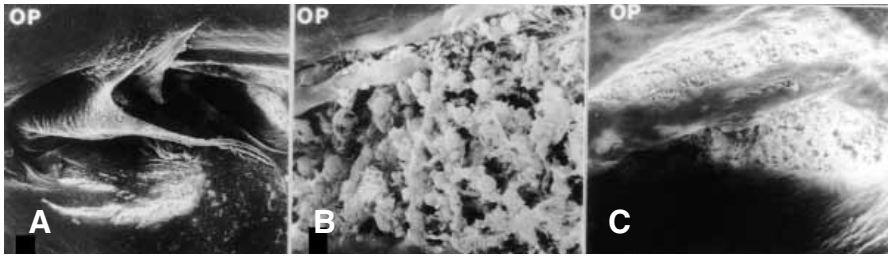


**Fig 4.** Scanning electron micrograph of the jugular vein of a dog that had a total hip replacement (OP). The jugular vein dilated >28% of baseline diameter during the experiment. **A,** Low-power magnification showing vein lumen and valve leaflet; note damage to vein wall in valve cusp. **B,** High-power magnification showing all of the elements of thrombus on the injured surface. **C,** Intermediate magnification shows tearing injury of endothelium within the valve cusp.

ceptions of the importance of calf DVT are their variable natural history, whether patients are symptomatic or asymptomatic, and whether the calf-vein thrombi are found incidentally on screening examinations of patients who are no longer at high risk or symptomatic outpatients who may be in early stages of their thrombotic event. Several studies reviewing isolated calf-vein thrombosis conclude that propagation occurs in 6% to 30% of postoperative and hospitalized patients, and early propagation occurs in 10% of symptomatic patients.[19,20] A prospective trial randomized patients with isolated calf DVT to either 5 days of intravenous heparin followed by no additional therapy or 3 months of anticoagulation.[21] Patients who were anticoagulated had no recurrent venous thromboembolic events, compared with a 29% recurrence in the no-treatment group. Meissner et al[18] followed 29 patients with isolated calf DVT as part of a natural history study. Seventy percent were symptomatic at diagnosis. Patients were followed clinically and with venous duplex for at least 1 year. Recanalization occurred rapidly, with the mean thrombus load reduced by 50% at 1 month. Twenty-three percent had post-thrombotic symptoms at 1 year. Venous valvular incompetence was progressive during follow-up, with reflex present in 24% of patients at 1 year. It is apparent that many patients with calf DVT will benefit from a shortened course of anticoagulation. I suggest a treatment strategy that incorporates the patient's ongoing risk factors and potential comorbidities for bleeding. If the etiology for the patient's calf DVT is identified and corrected, the patient should be at low risk for propagation and recurrence and can be followed with duplex. However, if the patient continues to be at risk or if the etiology is not defined, I would suggest a shortened course of anticoagulation for 3 months.

## ANTICOAGULATION IS BEST MANAGED BY PHYSICIANS

Anticoagulation is the recommended treatment for the majority of patients with venous thromboembolism. The adverse events of poor anticoagulation control are the consequences of excessive anticoagulation (hemorrhage) or subtherapeutic anticoagulation (thrombosis). Numerous studies have shown a strong relationship between time in therapeutic range and bleeding or thromboembolic rates. Therefore, time in therapeutic range can be used as a measure of overall effectiveness of the method of oral anticoagulation.

There is a widely held misconception that the physician most effectively manages the patient's anticoagulation. Although the majority of patients have their anticoagulation controlled by their personal physician, most physicians do not have an organized program of management, education, or follow-up. Several studies have shown that physician-controlled anticoagulation results in only 33% to 59% time in therapeutic range.[22-25]

If responsibility shifts from the physician to an anticoagulation clinic, there appears to be improvement in anticoagulation with time in therapeutic range increasing to 59% to 86%.[26-29] Reducing subtherapeutic and excessive anticoagulation avoids thrombotic and hemorrhagic complications, resulting in a cost savings of $860 to $1,320 per patient-year of therapy.[30]

With advancements in technology, point-of-care testing has developed and is a highly accurate and reliable technique.[31-33] Several small, portable instruments have been developed through which a patient can obtain his own prothrombin time from a simple finger stick. Patient self-testing has been studied, with the patient calling the blood-test result in to his physician's office for dosage adjustment, resulting in a further improvement (to 93%) in the percentage of time the patient is in the therapeutic range.[34]

Patients can be educated to use the point-of-care test results to manage their own dosage adjustments. Several studies have demonstrated that patient self-management also results in an improvement in the time in therapeutic range, 57% to 92%, which is generally better than management by a physician or an anticoagulation clinic.[22,25,28]

Taking anticoagulation management to the final level is the removal of all human judgement by virtue of a computer program. A computerized dosing regimen showed equivalent performance compared with an experienced medical staff in achieving a target international normalized

ratio of 2.0 to 3.0[35]; however, the computer demonstrated significantly better control when more intensive therapy was required (international normalized ratio, 3.0-4.5). Ageno and Turpie[36] studied patients with prosthetic cardiac valves who required anticoagulation with a computerized warfarin adjustment program. Results were similar to those achieved by manual regulation in terms of the percentage of patients maintained within the therapeutic range; however, the computerized program required 50% fewer dosage adjustments. Poller at el[37] reported results of a multicenter randomized study of computerized anticoagulant dosage and showed a 22% overall improvement of control with the computerized program compared with management by the medical staff.

## THE PROPHYLACTIC BENEFIT OF INTERMITTENT PNEUMATIC COMPRESSION IS LIMITED TO MECHANICAL ACCELERATION OF VENOUS RETURN

Intermittent pneumatic compression (IPC) is an effective mechanical method of DVT prophylaxis. Although a number of investigators have shown IPC to have favorable hematologic effects in reducing blood coagulability, predominately by increasing endogenous fibrinolytic activity,[38-40] many still believe that the benefit of IPC is limited to mechanical acceleration of venous return. Among researchers who recognize that IPC stimulates endogenous lytic activity, a second misconception is that the increased fibrinolytic activity is caused by endothelial release of tissue plasminogen activator. There are likely to be several reasons for these misconceptions. First, in studies denying the lytic effects of IPC, fibrinolytic activity was not routinely measured.[41] Components of the fibrinolytic system were used as surrogate endpoints, namely tissue plasminogen activator (t-PA) antigen and t-PA activity, as well as the rapid-acting inhibitor plasminogen activator inhibitor-1 (PAI-1). Because fibrinolytic activity is the result of activation of plasminogen to plasmin by both t-PA and urokinase type plasminogen activator (u-PA), and because assays for u-PA are not readily available, the true fibrinolytic effect will be missed if overall fibrinolytic activity is not measured. Moreover, if u-PA increases with IPC, there will be a down regulation of t-PA,[42] leading one to believe that there is no change in lytic effect because of minimal changes in t-PA antigen.

t-PA activity is, in fact, increased with IPC,[40] but not as a result of stimulation of t-PA antigen. IPC-enhanced plasma fibrinolytic activity is associated with a decrease in plasma t-PA antigen, PAI-1 antigen, and PAI-1 activity, but with an increase in t-PA activity caused by a marked decrease in PAI. Patients with post-thrombotic venous disease have significantly lower baseline and stimulated fibrinolytic activity.[40] If post-thrombotic patients are included in study samples but not recognized and stratified, the true fibrinolytic effects of IPC will be underestimated.

Another important but not well-recognized hematologic effect of IPC is the stimulation of tissue factor pathway inhibitor (TFPI). The initiating mechanism of blood coagulation is the tissue factor–dependent pathway. Tissue factor pathway is initiated when factor $VII_a$ is exposed to tissue factor, which leads to the tissue factor $VII_a$ complex, which activates factor X. Because TFPI is a major modulator of the tissue factor pathway, mobilization of pools of TFPI can be an important component of the antithrombotic effects of IPC. Chouhan et al[43] demonstrated a significant increase in TFPI and a decrease in plasma factor $VII_a$ with IPC, in both normal subjects and post-thrombotic patients. There are likely to be additional effects of IPC on the coagulation cascade that have yet to be investigated.

## THROMBOLYTIC THERAPY IS OF NO BENEFIT FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM

**Pulmonary embolism.** Thrombolytic therapy for venous thromboembolism is underused, in part, because of the misconception that therapy is of no proven benefit in patients with pulmonary embolism or venous thrombosis.

The early clinical trials sponsored by the National Institutes of Health (NIH) evaluating thrombolytic therapy versus standard anticoagulation for pulmonary embolism demonstrated consistent arteriographic, lung-scan, and hemodynamic improvement in patients treated with urokinase and streptokinase.[44,45] Lytic therapy rapidly improved the arteriographic and lung-scan findings during the resolution of pulmonary emboli ($P < .05$). Thrombolytic therapy also reduced pulmonary artery and right atrial pressure.

Although there was a 42% bleeding complication rate with lytic therapy, this was mostly caused by the multiple invasive procedures performed as part of the protocol. A 27% bleeding complication rate was observed in patients receiving standard anticoagulation. Because there was no difference in mortality between the two treatment groups, it is often concluded that lytic therapy was of no benefit. This is an inappropriate conclusion, because all patients with pulmonary emboli were randomized, not just those who were at risk of dying. Most patients with pulmonary emboli who are treated with anticoagulation do not die. Furthermore, these trials were not powered to show a mortality benefit.

Physiologic studies subsequently performed on patients in the NIH-sponsored trials evaluated the basic functional unit of the lung by measuring pulmonary capillary blood volume and oxygen-diffusing capacity.[46] At 1-year follow-up, significant benefit was found in patients treated with lytic therapy; such patients demonstrated greater pulmonary capillary blood volume and oxygen-diffusing capacity.

A 7-year follow-up evaluation was also performed, in which these patients were studied with right-sided heart catheterization.[47] Pulmonary artery pressures and pulmonary vascular resistance were measured with the patient at rest and exercising. Patients treated with lytic therapy had significantly lower pulmonary artery pressures and pulmonary vascular resistance both at rest and after exer-

cise. In addition, when the patient's functional status was evaluated, 73% (8/11) of patients treated with heparin were classified as New York Heart Association Functional Class III-IV, compared with 25% (4/12) of patients who were treated with a lytic agent.

Contemporary trials of thrombolytic therapy for pulmonary embolism have used urokinase and the newer lytic agent recombinant tissue plasminogen activator (rt-PA), which is nonantigenic and causes minimal, if any, allergic reaction. The newest agent to be studied is reteplase.[48] Petitpretz et al[49] treated 14 patients with acute life-threatening pulmonary embolism with large-dose urokinase delivered directly into the right atrium. Compared with pretreatment observations, 12 of the 14 patients showed a significant decrease in their pulmonary vascular obstruction and a significant reduction in their total pulmonary vascular resistance. There were no serious bleeding complications, and, interestingly, the majority of hemodynamic improvement occurred within the first 3 hours.

The Plasminogen Activator Italian Multicenter Study-2 investigators randomized 36 patients to receive either rt-PA as a 10-mg bolus followed by 90 mg infused over 2 hours or full anticoagulation with heparin.[50] Arteriographic improvement was significant in the rt-PA group but nonexistent in the group receiving heparin. Pulmonary artery pressures were significantly reduced in the lytic group and somewhat increased in heparin-treated patients. There was no difference in bleeding complications. Goldhaber and colleagues[51] addressed the important question of whether thrombolytic therapy for pulmonary embolism improved right-ventricular function and pulmonary perfusion as compared with anticoagulation alone. Significantly more rt-PA patients had improvement in right-ventricular wall motion and pulmonary perfusion. Interestingly, in the heparin-treated group, two patients had subsequent fatal pulmonary emboli and three had additional nonfatal pulmonary emboli. Recently, the results of a multicenter registry for pulmonary emboli were reported and should be helpful to all who hope to place thrombolytic therapy for pulmonary embolism into proper perspective. Konstantinides et al[52] reported that the overall 30-day mortality was significantly lower in the 169 patients who received thrombolytic agents than the 550 patients who received anticoagulation alone (4.7% vs 11.1%, $P = .016$). Primary thrombolysis was the only independent predictor of survival that reached statistical significance with multivariate analysis. The 30-day mortality after primary thrombolysis was also lower than that after anticoagulation by defining the patients on the basis of presenting characteristics such as age (<65 years, 3.0% vs 9.2%; >65 years, 7.1% vs 12.6%), arterial hypotension (4.1% vs 14.9%), arterial normotension (5.0% vs 8.1%), syncope (4.1% vs 17.9%), no syncope (4.9% vs 8.9%), no recent major surgery (2.9% vs 12.3%), and right-ventricular enlargement on echocardiography (4.7% vs 11.1%). Mortality was higher with thrombolysis than with heparin in postoperative patients (12.5% vs 7.6%). The clinical factors that were associated with higher mortality for both groups were the presence or absence of syncope (14.4% vs 7.8%, $P = .12$), arterial hypotension (12.6% vs 3.7%, $P = .021$), congestive heart failure (13.9% vs 7.7%, $P = .13$), and chronic pulmonary disease (17.1% vs 8.8%, $P = .032$). Among the other adverse events, major bleeding was higher (21.9% vs 7.8%), whereas recurrent pulmonary embolism was lower (7.7% vs 18.7%, $P < .001$) with thrombolysis than heparin. Recurrent pulmonary emboli were more common in patients with evidence of proximal DVT (17.2% vs 11.4%, $P = .06$) and the echocardiographic presence of right-sided thrombi (26.7% vs 15.9%, $P = .09$). Two intracranial bleeds and one hemorrhagic death occurred in each group.

**Iliofemoral DVT.** There is a broad-based misconception that removal of clot from the deep venous system of patients with iliofemoral DVT is of no value. It is also interesting to note that vascular surgeons in the United States do not hesitate to operate on patients with acute iliofemoral arterial thrombosis, but if the same or a greater volume of thrombus is located in the adjacent vein, there is general reluctance to operate, despite prospective randomized data demonstrating that thrombus removal from the iliofemoral venous system with surgical thrombectomy and arteriovenous fistula offers significantly better outcome than does anticoagulation alone.[53,54]

Catheter-directed thrombolysis is a pharmacologic approach designed to clear the thrombus from the iliofemoral venous system that can be applied to the majority of patients with iliofemoral venous thrombosis. We know that the post-thrombotic morbidity of iliofemoral DVT is severe[55,56] and that eliminating thrombus and restoring patency eliminates obstruction. Avoiding obstruction significantly reduces the virulence of the post-thrombotic syndrome.[3,4] In addition, it has been shown that early clot resolution offers the potential of preserving valvular function.[57]

During the past 13 years, 55 patients were treated with catheter-directed thrombolysis for occlusive iliofemoral and vena caval thrombosis at Temple University Hospital. The technique has evolved from urokinase infusions via a contralateral femoral and internal jugular-vein catheter placed into the clot to rt-PA at a 2-mg to 6-mg bolus and a 2-mg/h to 4-mg/h infusion, or the combination of an abciximab 0.25-mg/kg bolus + 0.125 μg/kg/min × 12 h + reteplase at 0.5 U/h, via an ultrasound-guided popliteal-vein or posterior tibial–vein catheter insertion. Forty-six of 55 patients (84%) had a successful outcome. Complications included puncture site hematoma in 8 patients (15%), blood transfusions required in 4 patients (7%), operative evacuation of a hematoma and repair of a common femoral vein required in 1 patient (2%), and 1 guidewire perforation of the common femoral vein (2%). Twenty-six percent of the patients were asymptomatic after therapy, and 52% had moderate improvement. Twenty-two percent of the patients were either unchanged or had only mild clinical improvement.

Mewissen et al[58] reported the largest series of catheter-directed thrombolysis for lower-extremity DVT. Their findings from the National Venous Registry and the

findings of Bjarnason et al[59] confirmed that 80% to 85% of patients with iliofemoral DVT can have a successful outcome when treated early in the course of their venous thrombosis. The complication rate remains relatively consistent and acceptable at 7% to 12%. Only one patient among three large series developed an intracranial bleed, and one patient died of a fatal pulmonary embolism during therapy.

After patient recruitment to the Venous Registry was completed, a study assessing health-related quality of life was designed to evaluate whether catheter-directed thrombolysis for iliofemoral DVT was associated with improved quality of life as compared with standard anticoagulation and whether health-related quality of life outcome in the thrombolysis group was related to lytic success.

An 80-item health-related quality of life questionnaire was developed and validated.[60] The validated questionnaire was then administered to 98 patients with iliofemoral DVT treated at least 6 months earlier. Sixty-eight patients who were treated with catheter-directed thrombolysis were identified through the National Venous Registry, and 30 patients who were treated with anticoagulation alone were identified through their physician or a medical-record review.[61]

The lytic group was younger (mean, 53 years) than the heparin group (mean, 61 years). After treatment, patients receiving catheter-directed thrombolysis reported better overall physical functioning ($P = .046$), less stigma ($P = .033$), less health distress ($P = .22$), and fewer post-thrombotic symptoms ($P = .006$) as compared with patients treated with anticoagulation alone. Within the lytic group, phlebographically successful lysis correlated with an improved health-related quality of life ($P = .038$). Interestingly, lytic failures and heparin treatment outcomes were similar. Failure of catheter-directed thrombolysis did not adversely affect outcome as compared with standard anticoagulation alone.

These data serve as an important foundation for the design of a randomized trial evaluating the treatment of patients with acute iliofemoral DVT. Such a trial should be multicenter and incorporate a strategy of thrombus removal versus anticoagulation alone. Preliminary discussions with the NIH have been instituted. If the NIH expresses the sentiment that such an effort would be worthwhile, an application will be forthcoming with the members of this organization forming the nucleus of the clinical investigators.

## SUMMARY

I have addressed a number of myths and misconceptions of venous disease, but there are many left to be discussed. There are not many randomized trials available from which to draw definitive conclusions. Many basic and clinical investigations lack the scientific rigor to allow firm conclusions; yet, the information can be enormously valuable. By objectively evaluating existing data and using available information integrated with known physiologic and pathophysiologic mechanisms, myths and misconceptions will disappear and understanding will be clarified. It is evident that "venous disease" encompasses many specialties, at both the basic science and clinical levels, which may contribute to the mystique of venous disease. Although the disciplines involved may be diverse, the principles underlying the management of venous disease remain simple.

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